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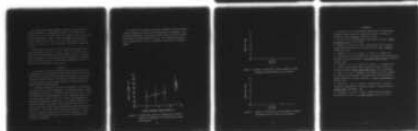
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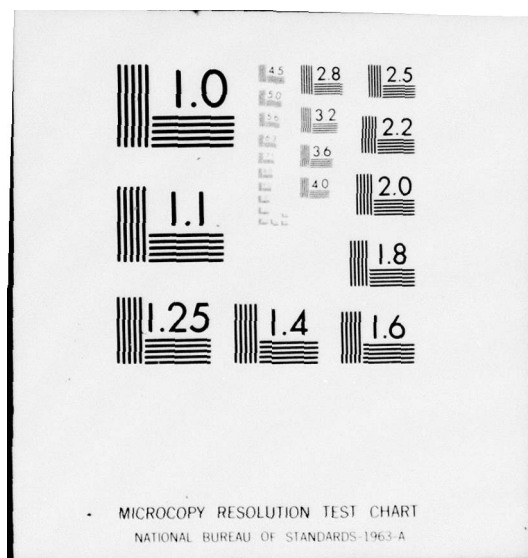
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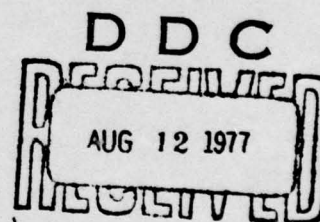
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OXYGEN CONSUMPTION, CEREBRAL OXYGEN TENSION, AND CEREBRAL CARBON DIOXIDE TENSION DURING AMBIENT HYPOXIA IN RHESUS MONKEYS

AEROSPACE MEDICAL RESEARCH LABORATORY
AND
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DAYTON, OHIO

AUGUST 1976



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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

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FOR THE COMMANDER



ROBERT E. VAN PATTEN
Assistant Chief
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Cerebral oxygen and carbon dioxide tensions as well as total oxygen consumption were monitored continuously in five conscious rhesus monkeys during exposure to ambient hypoxia. Ten experimental procedures on five monkeys demonstrated a linear relationship between ambient and cerebral oxygen tensions while oxygen consumption showed only a very slight dependence on ambient oxygen concentration. Cerebral carbon dioxide decreased slightly with hypoxia, and this decrease failed to be completely corrected with restoration of base line →		

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→ ambient and cerebral oxygen tensions. Thus, oxygen consumption was relatively constant during ambient hypoxia despite marked changes in cerebral oxygen tension as well as cerebral blood flow. ↗

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PREFACE

This study was accomplished at the Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. James A. Kennealy, Abbot T. Kissen, and Willi J. Buehring were the project officers for Aerospace Medical Research Laboratory. Alva A. Karl was the project engineer for the Systems Research Laboratories, Inc., 2800 Indian Ripple Road, Dayton, Ohio.

The authors are indebted to Ms Sharon Ward of the Systems Research Laboratories, Inc., and Mr. Marvin Souder of AMRL for the statistical analyses and technical assistance, respectively. The authors also express their gratitude to Ms Virginia Cormick, a student temporarily assigned to AMRL, for library and surgical assistance.

INTRODUCTION

Cerebral interstitial oxygen and carbon dioxide tensions in primates have been monitored by mass spectrometry (4,5). A technique has been developed at this Laboratory which involves the use of a stainless steel cranial implant to hold the Teflon^R membrane of a medical mass spectrometer firmly in an intracerebral position. The implant is well tolerated and allows repeated studies of conscious primates. The purpose of this experiment was to examine the relationship between intracerebral gas tensions and oxygen consumption during ambient hypoxia in conscious primates.

Relatively constant metabolic requirements at altitude have been demonstrated in humans. Oxygen consumption remains almost unchanged despite marked arterial hypoxemia (3,6). There may be some increase in carbon dioxide production and thus the respiratory quotient (1) at 10,000 feet, but this has not been consistently demonstrated even at 20,000 feet. Oxygen uptake is maintained by an appropriate increase in minute ventilation. This ventilatory response is influenced by several factors and seems to be slightly inhibited by a central response to hypoxia (8).

Recent work in this Laboratory has demonstrated that primate cerebral interstitial oxygen tension decreases almost linearly with ambient hypoxia. This is associated with a concomitant decrease in arterial blood oxygen tension. Cerebral interstitial $p\text{CO}_2$ decreases to a lesser extent with hypoxia.

It would seem, therefore, that oxygen consumption is independent of both cerebral $p\text{O}_2$ and $p\text{CO}_2$ and that it is maintained relatively constant by appropriate changes in minute ventilation. This experiment was designed to test the former hypothesis by monitoring both cerebral gas tensions and oxygen consumption in conscious monkeys during ambient hypoxia.

MATERIALS AND METHODS

Five rhesus monkeys, *M. mulatta*, weighing 4.2 to 7.5 kg were surgically prepared with a stainless steel cranial implant as previously

described (4). The implant is designed to firmly hold the Teflon^R catheter of a mass spectrometer in an intracranial position by means of an "O" ring. Each primate was allowed a minimum of two weeks recovery time prior to the experimental procedure.

On the morning of the procedure, the monkey was anesthetized with ketamine hydrochloride (Vetalar^R) 25 mg/kg intramuscularly. A Teflon^R coated catheter of a medical mass spectrometer was inserted through the surgical implant after the dura was penetrated with an 18 gauge needle. The mass spectrometer was the Medspect MS8 manufactured by Scientific Instruments, Baltimore, Maryland. The Teflon^R catheters were previously calibrated in an agitated saline bath at 37°C.

The animal was placed in a restraint chair (Figure 1) equipped with a sealed plexiglass helmet into which controlled, ambient oxygen concentration was introduced at 15 l/min as described below. A minimum anesthetic recovery time of three hours was allowed prior to initiation of the experimental procedure.

After recovering consciousness, the animal was exposed to gas mixtures including compressed air, 18%, 14%, and 10% oxygen in nitrogen. The mixtures of 18%, 14%, and 10% oxygen were administered in a random order and were separated in time by rest periods on air. Furthermore, the sequence of treatments was immediately preceded by periods on room air. Each exposure to a gas and each rest period was for about 15 minutes. This was sufficient to allow cerebral gas tensions to reach steady values. Each of the five monkeys was used in two experimental runs for a total of ten runs. The oxygen consumption was determined continuously in 1 minute increments for 6 to 8 minutes during each exposure, and the median value was used for data analysis. For purposes of data analysis, the observed value at 21% oxygen was taken to be the average value during all rest periods, excluding the pretreatment period.

The procedure for determining oxygen uptake was based upon the method described by Kissen and McGuire (7) with several significant modifications. The polarographic oxygen sensor was replaced by a dry

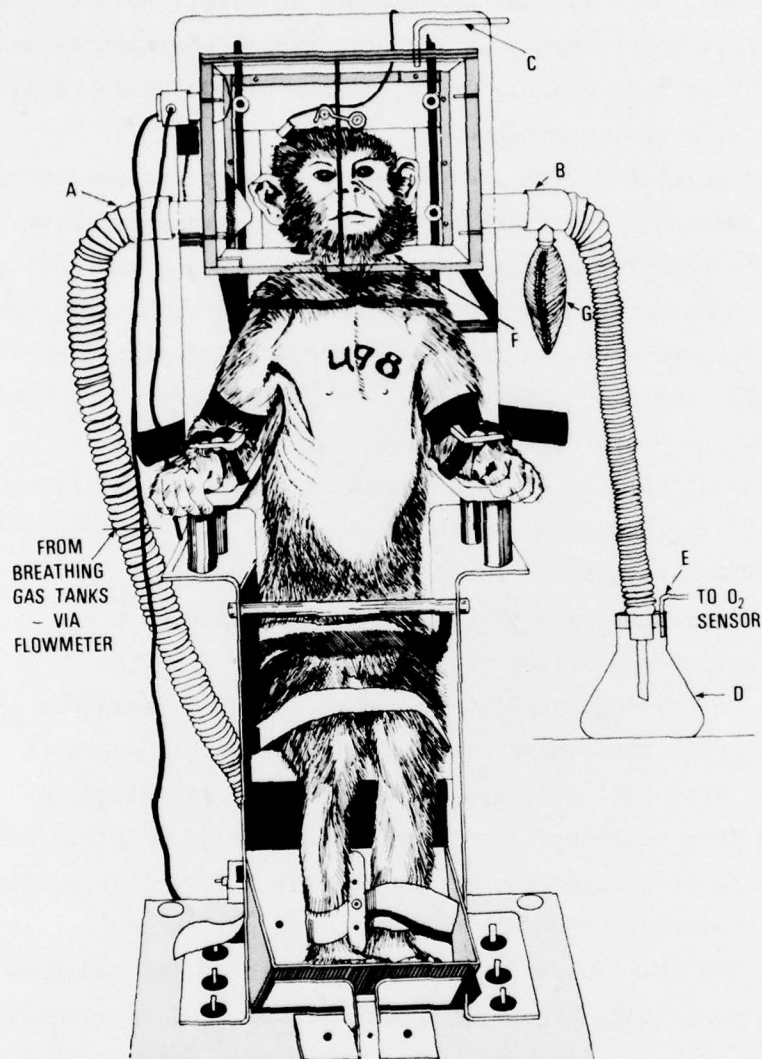


Figure 1. Rhesus Monkey Seated in Restraint Chair with Sealed Helmet

(A) breathing gas inlet port, (B) outlet port for expired air and introduced breathing gas mixture, (C) tube connected to pressure manometer to display breath pressure differentials and enable respiration rate determination rate, (D) mixing chamber for the expired air and introduced breathing gas diluent, (E) gas sampling tube, (F) soft rubber neck seal, (G) expired and introduced gas mixture reservoir to provide animal with transiently required extra breathing gas without creating negative pressure within the head enclosure

electrolyte oxygen sensor. In essence, the sensor functions as an ion-conducting cell whose solid (ceramic) electrolyte is composed mainly of stabilized zirconium oxide. When heated to 800°C (the operating temperature called for in this application), the oxygen in the lattice becomes mobile and an oxygen activity gradient creates an electric field having an open circuit potential proportional to the logarithm of the percent oxygen at the cathode and anode. Details regarding the physical characteristics and function of this type of cell have been provided by Hickam (2).

Another modification was in the manner of monitoring respiratory gas volumes. Rather than isolating and determining the mass flow of the exhaled gas exclusively, the present procedure involves monitoring a continuous, controlled flow of reference or sample breathing gas mixture through a plexiglass structure which encloses and atmospherically isolates the head of the animal (Figure 1). The volume of combined respiratory and diluent gas was determined by a flowmeter whose voltage output varies linearly with the mass flow of the gas mixture.

A simplified block diagram of equipment arrangement is shown in Figure 2. Pressurized tanks provided the reference and sample gas mixtures to the animal. Prior to each test, the flow rate of gas from the tank through the head enclosure was set at 15 l/min using the precalibrated flowmeter voltage output as the reference. In test, either one of two locations can be selected as sampling sites for the oxygen sensor by adjusting the three-way stopcock (A). Initially, a sample is drawn from a point (B) on the inlet side of the head enclosure through a drier and the oxygen sensor by a pump. The output of the oxygen sensor, after signal conditioning (C), involving anti-logarithm linearizing amplification, is adjusted to zero volts output. For data collection, the stopcock was repositioned, shifting the sampling site to the air mixing chamber on the downstream side of the head enclosure. The new output of the oxygen sensor, referenced to its previous zero setting, represents the ratio of inhaled to exhaled oxygen percentage values. The signal conditioned (D) flowmeter and

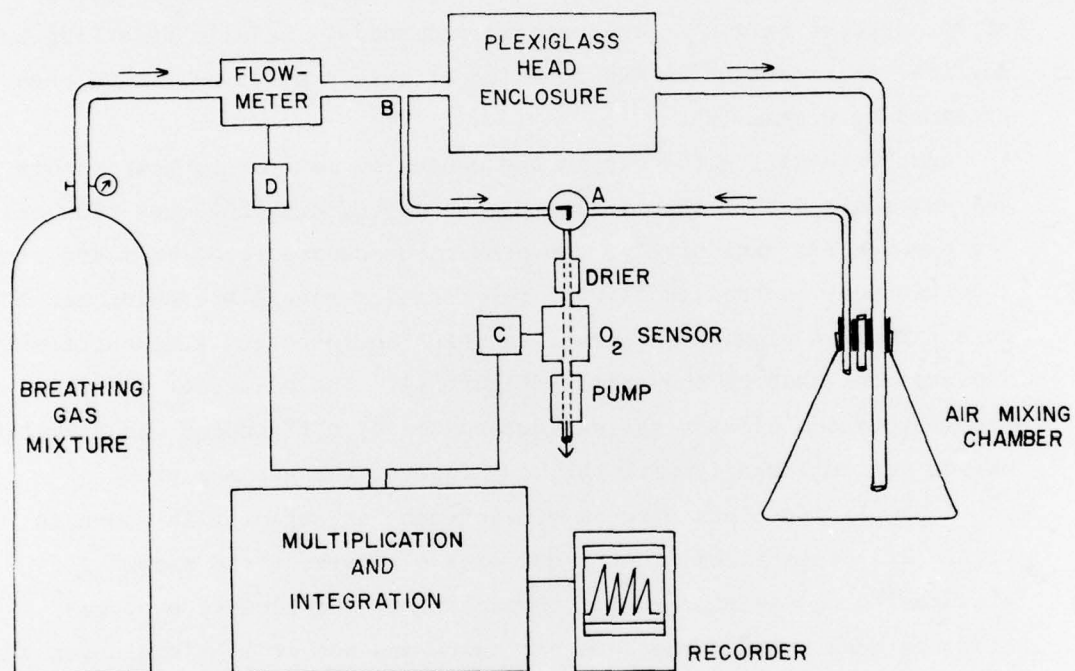


Figure 2. Block Diagram of Equipment Used to Analyze Oxygen Consumption
 [Refer to text for explanation of letter designations on the diagram.]

oxygen sensor outputs are conducted to a multiplication and integration circuit. Automatic, one minute integration of the product of mass gas flow and percent oxygen differential are recorded on a calibrated strip chart. The peaks of the integration curve are read directly as $\dot{V}O_2$ (cc/min).

RESULTS

With an ambient oxygen concentration of 21%, the cerebral pO_2 had an average value of 15.3 ± 2.9 mm Hg (95% confidence interval), and the carbon dioxide was 44.8 ± 1.9 mm Hg. With hypoxia, the pO_2 decreased to an average of 2.8 ± 2.2 mm Hg on 10% oxygen (Figure 3). Ambient oxygen concentration and the change in cerebral pO_2 were linearly related ($r = .82$). The pCO_2 decreased to an average of 37.9 ± 3.0 mm Hg on 10% ambient oxygen (Figure 4). The change in pCO_2 and the ambient oxygen concentration were quadratically related ($r = .71$).

The oxygen consumption, $\dot{V}O_2$, is weakly related to ambient oxygen concentration. The mean value was 57.4 ± 4.8 ml/min on room air and decreased to 51.4 ± 6.6 ml/min with hypoxia (Table 1). The correlation coefficient was $r = .26$ ($\alpha = .10$) so that 7% of the variance in $\dot{V}O_2$ is accounted for by ambient oxygen concentration.

Table 1
Mean Values and 95% Confidence Intervals for
Ten Exposures Using Five Monkeys

<u>AMBIENT OXYGEN CONCENTRATION</u>	<u>CEREBRAL pO_2 mm Hg</u>	<u>CEREBRAL pCO_2 mm Hg</u>	<u>$\dot{V}O_2$ ml/min</u>
21% (ROOM AIR)	15.3 (2.9)	44.8 (1.9)	57.4 (4.8)
18%	12.7 (1.8)	44.5 (1.4)	57.3 (5.9)
14%	7.2 (2.2)	42.5 (2.0)	53.3 (6.6)
10%	2.8 (2.2)	37.9 (3.0)	51.4 (6.6)

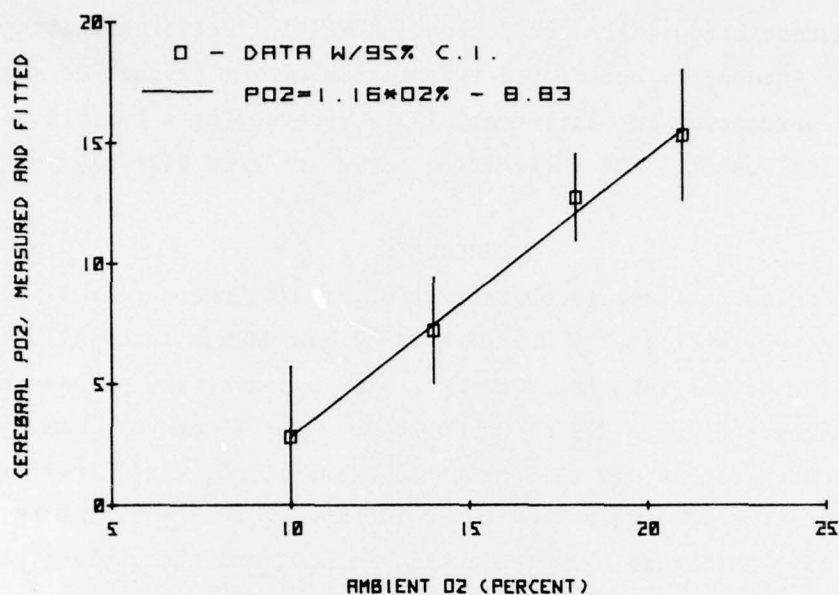


Figure 3. Cerebral pO₂ (mm Hg) Versus Ambient Oxygen Concentration in Ten Runs on Five Monkeys

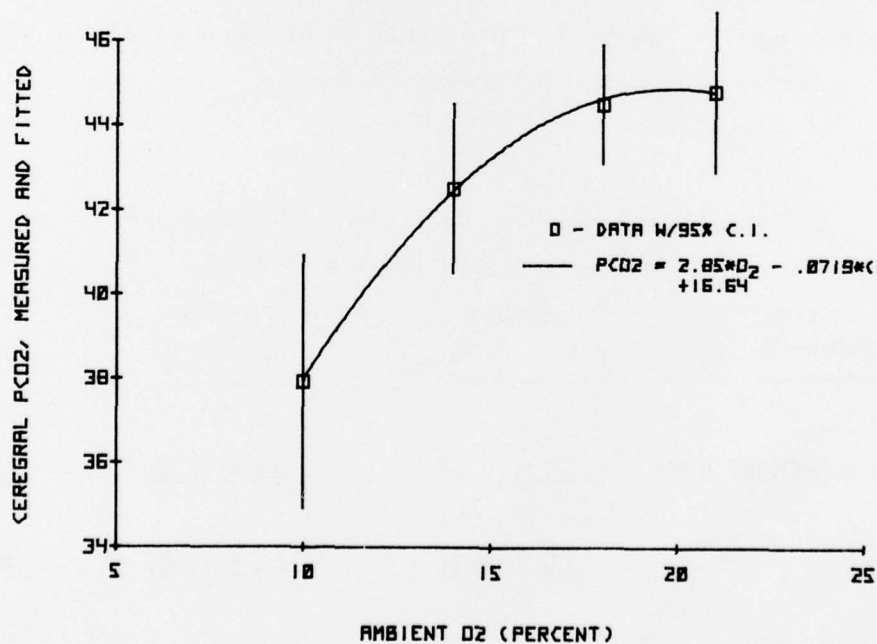


Figure 4. Cerebral pCO₂ (mm Hg) Versus Ambient Oxygen Concentration in Ten Runs on Five Monkeys

The relationship between changes in cerebral pO_2 and changes in oxygen consumption is illustrated in Figure 6. The correlation coefficient (r) is .48 so that 23% of the variance in $\dot{V}O_2$ is accounted for by cerebral pO_2 . Figure 7 shows the changes in pCO_2 plotted against changes in $\dot{V}O_2$. The r is .06, not significantly different from zero, and there is no other apparent relationship between pCO_2 and $\dot{V}O_2$.

Ambient hypoxia was noted to have a significant residual effect upon cerebral pCO_2 but not on the pO_2 or $\dot{V}O_2$. The values on 21% oxygen after each treatment are seen in Figure 5, and it is apparent that the residual effect increases with the severity of the hypoxia. Despite this effect, which is statistically significant, there is no significant residual effect on pO_2 or $\dot{V}O_2$.

DISCUSSION

The response of arterial blood pO_2 to ambient hypoxia has been investigated in several species including the rhesus; and it can be predicted that with a 10% ambient oxygen concentration, the arterial blood pO_2 is about 35 mm Hg. The values for cerebral interstitial pO_2 and pCO_2 reported here compare favorably with previous experimental data from this Laboratory.

The results substantiate the relative independence of intracerebral pO_2 and total oxygen consumption. The slight decrease in oxygen consumption at ambient O_2 of 10% may reflect several factors. Weiskopf has demonstrated a slight depression of the ventilatory response in man during hypoxia which is felt to be central and independent of peripheral chemoreceptor stimulation. It is most interesting that Weiskopf and Gabel calculated a tissue pCO_2 which was lower at a given arterial pO_2 during recovery from hypoxia than during induction of hypoxia. This is what we have found in our study (8). Another factor of possible significance is the relative sedation of most animals on 10% oxygen which may have caused a true depression of metabolic requirements.

In conclusion, it appears that oxygen consumption remains relatively constant during hypoxia despite several physiologic adjustments. The increased ventilation and increased cerebral blood flow may account for the decreased cerebral interstitial pCO_2 . The decreased interstitial pO_2 is expected in the face of a decreased concentration of inspired oxygen.

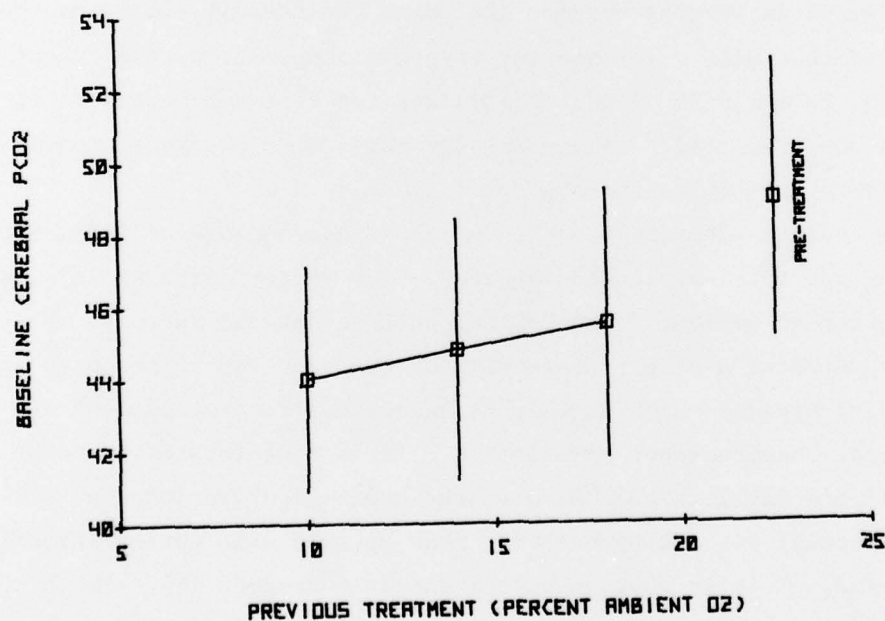


Figure 5. Cerebral pCO_2 (mm Hg) on Compressed Air Plotted Against the Immediately Preceding Ambient Oxygen Concentration

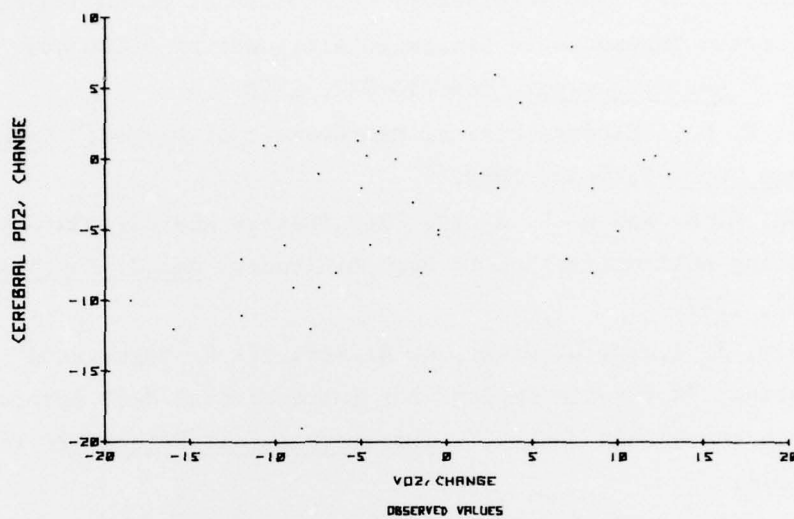


Figure 6. Changes in Cerebral pO₂ Versus Changes in Oxygen Consumption During Ten Runs on Five Monkeys

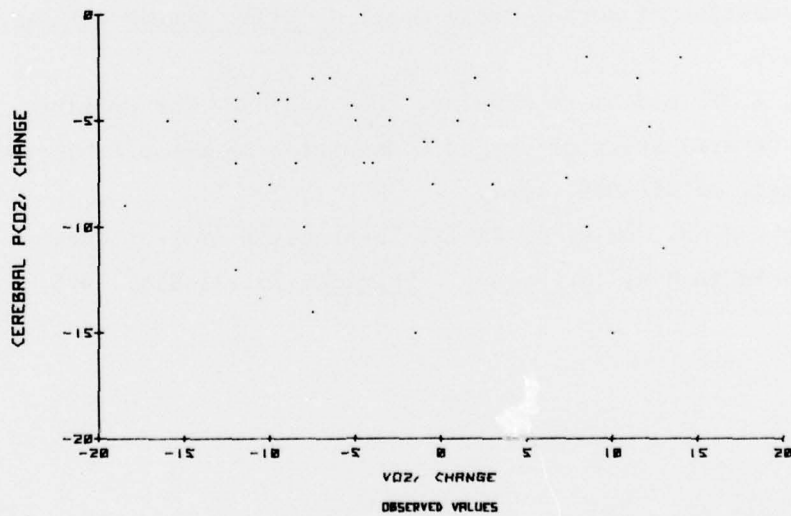


Figure 7. Changes in Cerebral pCO₂ Versus Changes in Oxygen Consumption During Ten Runs on Five Monkeys

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